Vortex Keratopathy Presumed Secondary to AZD9291

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A 58-year-old lifetime nonsmoking woman presented with a 6-month history of cough and was found to have a malignant pleural effusion. Diagnostic investigations revealed metastatic non–small-cell lung cancer (NSCLC) involving the left lower lung with pleural, nodal, and skeletal metastasis. Histologic examination confirmed a cytokeratin 7-positive and thyroid transcription factor-1 (TTF1)-positive adenocarcinoma. Molecular testing revealed a deletion in exon 19 of the epidermal growth factor receptor (*EGFR*) gene. She had no significant past history and was on no regular medications.

She was enrolled onto the first-line expansion cohort of the Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD9291 in Patients with Advanced Non Small Cell Lung Cancer who have Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent AURA - AZD9291 First Time in Patients Ascending Dose study, which treated EGFR-mutant NSCLC patients with AZD9291, a third generation tyrosine kinase inhibitor (TKI) at a dose of 160 mg daily. As part of the screening, ophthalmological assessment was performed, and no abnormalities were detected.

Five months after commencing AZD9291, she developed intermittent dry and itchy eyes consistent with keratoconjunctivitis sicca requiring topical lubricating solution for symptom relief (Fig. 1).

Restaging computed tomography scans after 3 months of treatment showed a partial response with reduction in size of the left lung mass and nodal metastases. Her pulmonary symptoms resolved, and she was able to resume working without any impingement on her functional status. Her intermittent keratoconjunctivitis sicca remained her only toxicity, but this was managed effectively with ophthalmic moisturizing drops.

Given ongoing issues with keratoconjunctivitis 8 months after commencement, further ophthalmological examination was performed. Vortex keratopathy or corneal verticillata were noted bilaterally with mild corneal deposits at the level of the basal epithelium in a whorl pattern, a classic feature of this condition.[1]

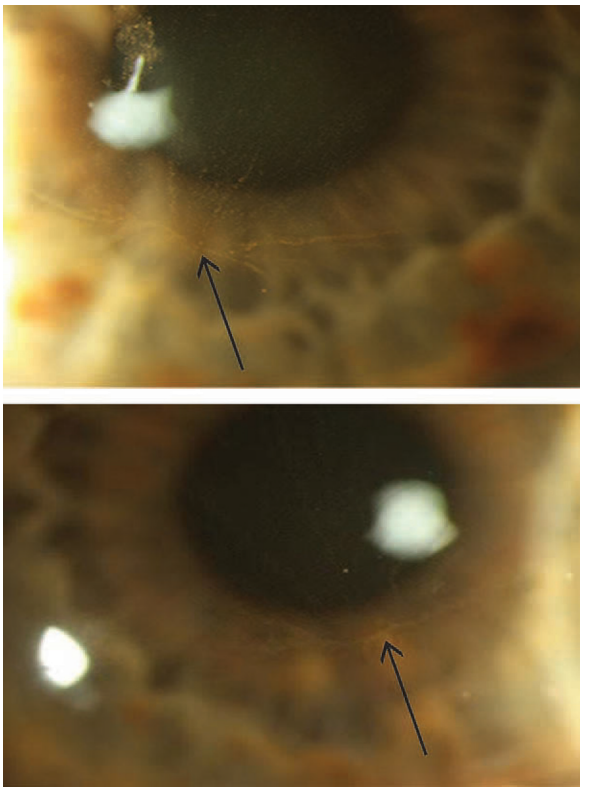

FIGURE 1. Corneal imaging 8 months after commencement of AZD9291 showing pigmented whorl-like pattern of grayish golden-brown deposits in the corneal epithelium (marked with black arrows).

Vortex keratopathy is a condition characterized by corneal deposits in a whorl or vortex pattern.[1] It is most often associated with amphiphilic medications, such as amiodarone, and chloroquine or metabolic disorders, such as Fabry's disease.[2,3] There are few reported cases of vortex keratopathy in patients receiving TKIs such as vandetanib

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and suramin (a drug used to treat sleeping sickness).[4,5] The underlying mechanism has been postulated to involve abrogation of normal corneal epithelial cell migration, a process dependent on epidermal growth factor signaling, although others have suggested its pathogenesis is related to the deposition of drug metabolites.

In view of the temporality of the development of vortex keratopathy with AZD9291, we postulate that this condition developed secondary to this novel TKI. In our patient, the keratopathy did not affect vision, and the patient was able to continue AZD9291 with concomitant topical lubricants.

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